REMARKS

The amendments to the Specification are necessary to correct proofreading/typographical errors in Reference Nos. 77 (cited on page 32, line 5), 91 (cited on page 32, line 19) and 199 (cited on page 33, line 22).

Claim 71 has been canceled, Claims 67-70, 72-74, 76 and 79-84 have been amended, and new Claims 85-90 have been added, to point out with greater clarity and particularity the subject matter regarded by the Applicants as their invention. Applicants respectfully submit that the amendments to Claims 67-70, 72-74, 76, and 79-84, and new Claims 85-90, are supported throughout the Specification.

Claims 68, 70, 72, 76 and 79-84 have been amended to delete references to methods comprising the use of MN/CA IX inhibitors to detect "activated CA IX" and/or hypoxic conditions, and are instead directed to methods comprising the use of MN/CA IX inhibitors to detect MN/CA IX. Support for those amendments can be found at the least in the original Claim 67. Applicants respectfully point out that said amendments are being made without prejudice, in view of a detailed set of claims analogous to those of unamended Claims 68, 70, 72, 76 and 79-84 in copending, commonly owned U.S. Serial No. 11/222,986. Applicants respectfully reserve the right to file comparable claims to those of unamended Claims 68, 70, 72, 76 and 79-84 in a continuation application to protect the invention commensurate with the scope as originally filed.

For greater clarity and particularity, Claim 68 has also been amended to agree with its antecedent basis in Claim 67, to specify that the decisions on treatment are made "in view of the level of said MN/CA IX" (rather than "the presence of said MN/CA IX").

Compounds

Independent Claims 67, 69, 70 and 83 have been amended for greater clarity and particularity to specify that the MN/CA IX inhibitors used according to the claimed methods are organic heterocyclic and aromatic compounds (Claims 67 and 69), cell membrane-impermeant heterocyclic and aromatic organic compounds (Claim 70), or cell membrane-impermeant heterocyclic and aromatic sulfonamides (Claim 83).

Support for those amendments can be found throughout the Specification, for example at least at page 11, lines 22-29, particularly at page 11, lines 22-24, which reads: "Said CA IX-specific inhibitors are preferably organic, more preferably aromatic or heterocyclic, and still more preferably an aromatic sulfonamide or a heterocyclic sulfonamide." Other exemplary support for those amendments can be found at least at page 53, line 25 to page 54, line 22 ["Design of Membrane-Impermeant Sulfonamide Inhibitors of CA IX"].

Support for amended Claims 72-74 and new Claims 85-90, wherein said diagnostic/prognostic method, or wherein said imaging method, comprises the use of an organic heterocyclic or aromatic CA IX inhibitor that is a heterocyclic or an aromatic sulfonamide, preferably wherein the sulfonamide is selected from the group consisting of Compounds 1-91, or preferably a cell-membrane impermeant pyridinium derivative of an aromatic or heterocyclic sulfonamide, can be found throughout the Specification, for example, at least at page 1, lines 14-20; at page 42, lines 16-31; and in the Abstract at page 93, which reads in pertinent part:

> Preferred CA IX-specific inhibitors are aromatic and heterocylic sulfonamides, preferably that are membrane-impermeant. Particularly preferred CA IX-specific inhibitors are pyridinium derivatives of such aromatic and heterocyclic sulfonamides. The CA IX-specific inhibitors of the invention can also be used diagnostically/prognostically for preneoplastic/neoplastic disease, and for imaging use, for example, to detect precancerous cells, tumors and/or metastases.

[Abstract, page 93, lines 8-14.]

In new Claim 84, the membrane-impermeant sulfonamide is a "positively-charged, membrane-impermeant aromatic or heterocyclic sulfonamide." In new claim 86, the MN/CA IX specific sulfonamide inhibitor is "selected from Compounds 27-70." Support for new Claims 84 and 86 can be found throughout the Specification, for example, at least at page 28, lines 20-26 (Claims 84 and 85) and at page 62, line 12 to page 65, line 4 (Claim 86).

Enzymatic Screening Assays

Independent Claims 67, 69, 70 and 83 have further been amended for greater clarity and particularity to be directed to methods using MN/CA IX inhibitors that have been determined to be potent against MN/CA IX (wherein the inhibition constant K_I is determined to be less than about 50 nanomolar). Support for those amendments can be found throughout the Specification, for example, at least at page 1, lines 17-20; at page 8, lines 15-30; at page 10, lines 24-27; at page 17, lines 1-3; and at page 74, lines 23-26.

Independent Claims 67, 69, 70 and 83 have been still further amended for greater clarity and particularity, to specify that the potent CA IX inhibitors have also been determined to be selective for MN/CA IX over other carbonic anhydrase (CA) isozymes (or isoforms) in enzymatic screening assays. In Claims 67 and 69, the MN/CA IX potent inhibitors are determined to be MN/CA IX-specific if said inhibitor is a more potent inhibitor of MN/CA IX enzymatic activity than of that of each of the widely distributed carbonic anhydrase (CA) isozymes (or isoforms) in the group consisting of CA I, CA II and CA IV. Support for those amendments can be found throughout the Specification, for example, at least at page 8, line 24 to page 9, line 7; at page 12, lines 3-6; at page 17, lines 14-17; and at page 76, lines 1-3 (original Claim 12).

In Claims 70 and 83, the CA IX potent inhibitors are both selected from the group consisting of cell membrane-impermeant, heterocyclic and aromatic compounds, and have been determined to be an MN/CA IX-specific inhibitor if it is a more potent inhibitor of MN/CA IX enzymatic activity than of that CA IV, a membrane-bound carbonic anhydrase with high enzymatic activity. Support for those amendments to Claims 70 and 83 can be found throughout the Specification, for example, at least at page 8, lines 3-12 and at page 17, lines 17-20. The Specification points out that when membrane-impermeant MN/CA IX-specific inhibitors are the subject, it is "particularly important . . . that the . . . inhibitor . . . [be] more potent . . ." in inhibiting the MN/CA IX enzymatic activity than that of another membrane bound CA, that is, CA IV, which is a widely distributed membrane bound CA. On that point, the Specification states at page 17, lines 17-20:

> **Since both CA IX and CA IV are membrane bound CAs**, it is **particularly important that the membrane-impermeant CA IX-specific inhibitor compounds are more potent inhibitors of MN/CA IX enzymatic activity than of the enzymatic activity of CA IV.**

[Emphasis added.] CA I and II are cytosolic CA isozymes (as noted at least at page 6, lines 10-13 of the Specification), and due to their intracellular location, should not be affected by membrane-impermeant CA inhibitors.

Additional Amendments

Claim 76 has been amended to depend from independent Claim 70, instead of canceled Claim 71.

Support for the amendments to Claims 79-82, wherein the diagnostic/prognostic method is used as an aid in patient therapy selection, such as MN/CA IX-targeted therapy, or to monitor the status of a cancer patient, can be found throughout the Specification, for example, at least at page 22, line 28 to page 23, line 5; at page 26, lines 9-16; at page 27, line 7 to page 28, line 14; and at page 93, lines 15-19 (Abstract).

Support for the amendments to the preamble to Claim 83, wherein the claimed method is "[a] method of imaging a tumor or tumors and/or metastases that express MN/CA IX in a patient," can be found throughout the Specification, for example, at least at page 25, lines 7-9, which reads: "This invention further concerns methods for imaging tumors and/or metastases that express CA IX in a patient comprising the administration of a CA IX-specific inhibitor linked to an imaging agent to said patient."

Conclusion to Remarks

Applicants respectfully conclude that no new matter has been entered by any of the above amendments.

I. Species Election

Applicants affirm the provisional election of species made with traverse to the species of Compound 71, during a telephone conversation of the undersigned

Attorney for the Applicants with the Examiner on January 22, 2007. Applicants acknowledge and thank the Examiner for his subsequent withdrawal of that provisional election of species [Instant Office Action, at page 2].

II. Claim Objections

Claims 70-84 are objected to because "it is suggested that Applicants either amend Claims 67-69 to recite 'MN/CA IX' or amend Claims 70-84 to 'CA IX' for consistency purposes." [Office Action, at page 3.] Applicants respectfully point out that the claims as amended all refer to "MN/CA IX" only.

Claim 68 is objected to under 37 CFR 1.75(c), "as being of improper dependent form for failing to further limit the subject matter of the previous claim." Applicants respectfully traverse said objection, respectfully pointing out that Claim 68 further limits Claim 67, in that Claim 68 refers to the situation wherein a poor prognosis has been made based on the level of MN/CA IX in the sample, and wherein treatment decisions are then made in view of said MN/CA IX level.

Applicants respectfully request that the Examiner reconsider and withdraw the subject objections in view of the amendments to Claims 70-84 and the above explanation in regard to Claim 68.

III. Claim Rejections – 35 USC 112, ¶2 [Page 3]

Claim 68 stands rejected under 35 USC § 112, second paragraph, as being indefinite. The Office Action states at page 3: "Claim 68 recites the limitation 'CA IX activated by hypoxic conditions' in the first line. However, . . . , there is insufficient antecedent basis for this limitation. . . ." Applicants respectfully point out that Claim 68 has been amended to delete the phrase in question ("CA IX activated by hypoxic conditions"), and to replace the second phrase "said hypoxic conditions" with "said MN/CAIX." Applicants respectfully submit that the claim amendments overcome the instant 35 USC 112, second paragraph rejection, and respectfully request that the Examiner withdraw the instant rejection.

IV. 35 USC 112, ¶1 (Written Description)

Claims 67-72 and 76-84 stand rejected under 35 USC 112, first paragraph, as

> failing to comply with the written description requirement. . . .
>
> . . . .
>
> . . . [A] CA IX specific inhibitor "useful for diagnosing a tumor" does not distinguish any . . . particular compound from others having the same activity or function and as such does not satisfy the written-description requirement.

[Office Action, pages 4-5.] Applicants respectfully traverse this rejection, first respectfully pointing out that the subject claims are original claims and as pointed out by the Manual of Patent Examining Procedures (MPEP) § 2163 (II)(A): "[R]ejection of an original claim for lack of written description should be rare." [Emphasis added.]

Numerous cases hold that an "original claim," that is, one contained in the specification when it is filed, complies with the Section 112 invention description requirement. [See, for example, In re Koller, 204 USPQ 702 (CCPA 1980); Union Oil Co. of California v. Atlantic Richfield Co., 54 USPQ2d 1227 (Fed. Cir. 2000).] For example, the Court of Customs and Patent Appeals (CCPA)[1] in In re Smith, 481 F.2d 910, 178 USPQ 620 at 623 (CCPA 1973) stated: "Where the claim is an original claim, the underlying concept of insuring disclosure as of the filing date is satisfied, and the description requirement has likewise been held to be satisfied."

The Manual of Patent Examining Procedure in Section 2163(I)- (II) states:

> There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the

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1. The CCPA is a predecessor court to the Court of Appeals for the Federal Circuit. In the Federal Circuit's first reported opinion, South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982), the Federal Circuit adopted as binding precedent "the holdings of our predecessor courts, the United States Court of Claims and the United States Court of Customs and Patent Appeals [CCPA]. . . ."

> disclosure a description of the invention defined by the claims").
>
> . . . .
>
> Consequently, rejection of an original claim for lack of written description should be rare.

[Emphasis added.]

The PTO's Written Description Guidelines [Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001)] similarly indicate that there is a "strong presumption that an adequate written description of the claimed invention is present when the qpplication is filed, consistent with In re Wertheim, supra.

> The Guidelines emphasize that the burden of proof is on the **examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the burden of going forward with contrary evidence to the applicant**.

[*Id*. at page 1100, col. 3; emphasis added.] Applicants respectfully submit that the Examiner has not introduced sufficient evidence to shift the initial burden of proof to the Applicants, but if hypothetically that burden had been shifted, the Applicants would have overturned that burden as explained in the discussion below in view of the amendments for particularity and clarity of the independent claims.

Independent Claims 67, 69, 70 and 83 as amended describe the claimed CA IX-specific inhibitors with greater clarity and particularity, as organic aromatic and heterocyclic compounds that have been screened to be potent and selective inhibitors of CA IX enzymatic activity. Independent Claims 70 and 83 have been amended to define the CA IX-specific inhibitors with greater particularity as cell membrane-impermeant aromatic and heterocyclic compounds, or as cell membrane-impermeant aromatic and heterocyclic sulfonamide compounds – those compounds that are

> selected from the group consisting of heterocyclic and aromatic sulfonamides, and wherein said compound is determined to be a potent inhibitor of MN/CA IX enzymatic activity in a screening assay comprising determining the inhibition constant K_I of said compound; wherein if said

> inhibition constant K_I is determined to be less than about 50 nanomolar, said compound is determined be a potent inhibitor of MN/CA IX enzymatic activity; . . .

[Added proviso of Claims 70 and 83.] Applicants respectfully submit that they were in possession of the clamed genus of CA IX-specific aromatic and heterocyclic sulfonamides that have been screened for both potent and specific inhibition of CA IX enzymatic activity at the application's priority date.

The Specification also provides direction for one of skill in the art for the selection and/or design of heterocyclic and aromatic organic CA IX-specific inhibitors other than sulfonamides, according to the methods of amended Claims 67 and 69. For example, the Specification teaches a number of important differences between the active site cavity of MN/CA IX's catalytic domain and that of the other widely distributed relevant carbonic anhydrase isoenzymes, such as, CA I, CA II, and CA IV. Such differences between the active sites of MN/CA IX and the other widely distributed, relevant CA isozymes taught by the Specification can be used by those of skill in the art to pick other organic heterocyclic and aromatic compounds to test in the representative screening assays disclosed in the Specification, for the functionalities required by the claimed methods.

A particularly significant difference between MN/CA IX's active site and that of other relevant CA isozymes is that MN/CA IX's active site is "larger than that of the other investigated isoenzymes." [Specification, page 4, lines 1-4.] The larger size of MN/CA IX's active site explains potentially why more bulky compounds that strongly inhibit MN/CA IX were weak inhibitors of CA I, II and IV. The larger active site cavity of MN/CA IX is explained at page 53, line 32 to page 54, line 8, in relation to CA II, wherein that important difference is attributed to the amino acid at position 131, which is Phe for CA II, and Val for CA IX.

Another important amino acid residue difference between MN/CA IX and CA II is that at position 132, which is Gly in CA II, and Asp in CA IX.

> This residue is situated on the rim of the hydrophilic half of the entrance to the active site of hCA II (and presumably also of hCA IX) and it is critical for the interaction with inhibitors possessing elongated molecules. . . . Strong hydrogen bonds involving the CONH moiety of Gly 132 were

> shown to stabilize the complex of this isozyme with a p-aminoethylbenzenesulfonamide derived inhibitor. . . . In the case of hCA IX, the presence of aspartic acid in this position at the entrance of the active site may signify that: (i) stronger interactions with polar moieties of the inhibitor bound within the active site should be possible, since the COOH moiety possesses more donor atoms; (ii) this residue may have flexible conformations, fine-tuning in this way the interaction with inhibitors.

[Specification, page 54, lines 9-19; emphasis added.] The instant Specification for the first time provides a structure/function analysis of the CA IX active site which can be used in the design of CA IX-preferential aromatic and heterocyclic inhibitors.

Inapplicability of Case Law Cited

Applicants respectfully distinguish the circumstances of the cases cited by the Examiner at pages 4-6 of the Office Action in support of the written description rejection in the paragraphs below. Applicants respectfully note the commonality of the cases cited as being inapposite to the instant situation in that each concerns composition of matter claims to DNA sequences that each encode a human protein, wherein the DNA sequence (gene) had not been yet isolated, whereas the instant claims are method claims that use known organic heterocyclic or aromatic compounds that have certain functionalities determined by screening assays disclosed in the Specification.

Enzo Biochem and Eli Lilly

The Federal Circuit in Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316 at pages 1328-1329 (Fed. Cir. 2002) refers in one paragraph to the phrases "an anti-inflammatory steroid" and "an antibiotic penicillin" (mentioned in the Office Action at pages 5-6) as failing to distinguish "any steroid from others having the same activity" and "a particular penicillin molecule from others having the same activity," respectively. Applicants respectfully emphasize that the context of that one paragraph in Enzo Biochem, wherein those two phrases appear, is very different from that of the instantly pending claims. The context of that paragraph was the Federal Circuit's response to

"Enzo's additional argument that the written description requirement for the generic claims is necessarily met as a matter of law because the claim language appears in ipsis verbis in the specification." [Id.] In that context, the Federal Circuit was using the two phrases as examples of "mere indistinct words" whose "appearance in a specification or a claim, even an original claim, does not necessarily satisfy . . . [the written description] requirement." [Id.; emphasis added.]

Applicants respectfully point out that the Enzo Biochem case actually provides support for the pending claim language by analogy to the Federal Circuit's acknowledgement therein that "hybridization to disclosed organisms may meet the PTO's [Written Description] Guidelines stating that functional claiming is permissible when the claimed material hybridizes to a disclosed substrate." [Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316 at 1328 (Fed. Cir. 2002); emphasis added.] Applicants respectfully submit that the claimed methods of the instant invention have analogous functional language requiring in essence that the organic heterocyclic and aromatic compounds have a better fit into the active site cavity of MN/CA IX's carbonic anhydrase catalytic domain, than of the active site cavities of other relevant widely distributed carbonic anhydrase isozymes, for example, CA I, CA II and CA IV, (Claims 67 and 69), as determined by the screening assays disclosed in the Specification that indicate comparative potency of inhibition of enzymatic activity. Then, hybridizing to a "disclosed substrate" is analogous to having an organic heterocyclic or aromatic compound fit within the active site of MN/CA IX, whose amino acid sequence is known, and whose attributes that would be significant to one of skill in the art are disclosed in the Specification.

The Federal Circuit in Enzo Biochem Inc. V. Gen-Probe Inc., 296 F.3d 1316 at 1327 (Fed. Cir. 2002) also considered whether the three deposited [at the American Type Culture Collection (ATCC)] nucleotide sequences were "representative of the scope of the genus claims . . . ," and distinguished the situation in the Enzo case from that in Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) where

> a disclosure of the sequences of a rat cDNA was not descriptive of the broader invention consisting of mammalian and vertebrate cDNA. . . . [in that in] Eli Lilly, the

> specification and generic claims to all cDNAs encoding the vertebrate or mammalian insulin **did not describe the claimed genus because they did not set forth any common features possessed by members of the genus that distinguished them for others.**

[Id., emphasis added.] In distinction from the Eli Lilly case, the instantly claimed invention does set forth such "common features possessed by members of the genus," that is, that the organic heterocyclic and aromatic compounds useful in the claimed methods are potent inhibitors of MN/CA IX enzymatic activity, having inhibition constants (K_1) determined by the disclosed screening assays to be less then 50 nanomolar. Further, the organic heterocyclic and aromatic compounds useful in the claimed methods show other common features, for example, being more potent inhibitors of MN/CA IX enzymatic activity than of that of the other relevant widely distributed CA isozymes -- CA I, CA II and CA IV (Claims 67 and 69) -- or in the case of cell membrane-impermeant MN/CA IX-specific heterocyclic and aromatic organic compounds (Claim 70), being more potent inhibitors of MN/CA IX's enzymatic activity than of CA IV's enzymatic activity.

The "genetic material" found to lack written description in Eli Lilly was the human insulin gene for which the native DNA sequence was **not** provided. The Eli Lilly case is further clearly distinguishable from the instant application in that the involved U.C. patent claims, **as compositions of matter**, recombinant plasmids with cDNA encoding for (1) rat insulin, (2) human insulin, and (3) vertebrate and mammalian insulin. However, the UC inventors had only discovered the sequence for proinsulin (PI) and preproinsulin (PPI) **rat** insulin.

Applicants respectfully distinguish the Eli Lilly case from that of the instant application, in that the Applicants are not claiming as compositions of matter, that is, as compounds per se, the organic heterocyclic and aromatic compounds (Claims 67, 68 and 69), particularly heterocyclic and aromatic sulfonamides (Claims 87-90), more particularly cell membrane-impermeant heterocyclic and aromatic compounds (Claims 70 and 76-82), including cell membrane-impermeant aromatic or heterocyclic sulfonamides (Claims 72-75 and 83-86), further including positively-charged, cell membrane-impermeant aromatic and heterocyclic sulfonamides (Claim 84), and further

including cell membrane-impermeant pyridinium derivatives of aromatic and heterocyclic sulfonamides (Claims 73 and 85). Applicants are instead claiming the use of said compounds in the claimed methods. Said organic heterocyclic and aromatic compounds, that are useful in the claimed methods, are those that share certain **specific functionalities**, that is, for example, as indicated above that inhibit CA IX's enzymatic activity in a screening assay with an inhibition constant K_1 less than about 50 nanomolar, and that are more potent inhibitors of MN/CA IX's enzymatic activity than that of each of CA I's, CA II's and CA IV's (Claims 67-69).

Fiddes v. Baird

The Office Action at page 5 refers to Fiddes v. Baird, 30 USPQ2d 1481 (Bd. Pat. App. & Int'f 1993) as concerning

> claims directed to mammalian FGF's . . . [as being] found unpatentable, due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences.

However, in Fiddes v. Baird, the applicant Baird was claiming a recombinant DNA molecule that encodes "mammalian" fibroblast growth factor (FGF) wherein the specification disclosed only a **146 amino acid sequence for bovine pituitary FGF but no sequence for the native DNA,** that is, in Fiddes v. Baird, the specification provided no native DNA sequence, bovine or otherwise. The Board in Fiddes v. Baird at pages 1483-1484 relied upon In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993) for the holding that the

> knowledge of the amino acid sequence of a protein coupled with the established relationship in the genetic code between a nucleic acid and the protein it encodes would not establish possession of the gene encoding that protein . . .
>
> . . . .
>
> Turning to Baird's description of the DNA sequence encoding FGF, we note that he did not postulate the correct sequence for the naturally occurring gene but rather a **theoretical DNA sequence for the bovine pituitary FGF out of the myriad possibilities. . . . Thus, Baird was not**

> **in possession of the naturally occurring gene for bovine pituitary FGF or any other gene for any mammalian FGF** at the time of filing of the . . . **application**

[Emphasis added.]

Then, in Fiddes v. Baird, the applicant did not have possession of or a single member of the claimed genus of DNA sequences encoding mammalian FGFs. In contrast, the instant application provides any number of examples of organic heterocyclic and aromatic compounds that have the functionality necessary to be used in the claimed methods. Further, the instant application describes screening assays to determine whether a specific organic heterocyclic or aromatic compound has the required functionality for use in the methods of the invention.

Amgen v. Chugai

Similarly Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) concerns a claim to "a purified and isolated DNA sequence" that encodes human erythropoietin (EPO). The Federal Circuit held that

> when an inventor is unable to envision the detailed constitution of a **gene** so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the **gene** has been isolated.

[Emphasis added.] Again, in Amgen v. Chugai, the claim in controversy is a composition of matter claim to a DNA sequence that encodes a human protein, wherein the inventor (Fritsch) had not isolated any DNA sequence but only had a potential method for isolating it. Again, the instant invention is distinguishable in that the instant claims are not to a DNA sequence that encodes a human protein, which sequence (gene) had never before been isolated, but to method claims that use known organic heterocyclic and aromatic compounds, wherein many representative compounds are identified and shown to have the required functionalities for the claimed methods by disclosed screening methods.

Fiers v. Revel

Fiers v. Revel, 25 USPQ2d 1601 (Fed. Cir. 1993), also relied upon by the Examiner, also concerns a claim (actually an interference count) to DNA encoding a human protein – "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." [Id. at 1603.] The Federal Circuit found in Fiers v. Revel that an inventor was not entitled to priority from his foreign application filing date in the context of an interference, because no nucleic acid sequence data was provided, only a potential method to isolate it. Applicants respectfully distinguish the facts of the instant invention from that of Fiers v. Revel, in that in Fiers, again a particular DNA that encodes a human protein is being claimed, wherein no nucleic acid encoding for that protein had been isolated, whereas in the instant invention, the heterocyclic and aromatic organic compounds are not being claimed as particular compositions of matter, but for use in the claimed methods, and a large number of representative compounds have been shown to have the necessary functionality for the claimed methods.

Written Description Conclusion

Applicants respectfully conclude that the Specification meets the written description requirement of 112, 1st paragraph, for Claims 67-72 and 76-84, and in accordance with the PTO's Written Description Guidelines, satisfies the written description requirement for a claimed genus, not only

> through sufficient description of a representative number of species by actual reduction to practice . . . [but also] by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. . . .

[Fed. Reg., Vol. 66, No. 4 (Jan. 5, 2001), at page 1106 (col. 3).]

Applicants respectfully submit that the claims as amended meet the written description requirement for the claimed methods, comprising the use of a genus

of heterocyclic and aromatic CA IX-specific inhibitors, and respectfully request that the Examiner withdraw the instant 35 USC 112, first paragraph rejection.

V. 35 USC 112, ¶1 (Enablement)

> Claims 67-84 stand rejected under 35 USC 112, first paragraph,
>
> because the specification, while being enabling for a method of diagnosing cancer and/or hypoxia in a tissue and in vivo imaging of a tumor and/or hypoxic tissue in a patient comprising administering a labeled antibody which specifically binds CA IX, wherein overexpression of CA IX is indicative of cancer, does not reasonably provide enablement for [such] a method . . . comprising administering a CA-IX specific inhibitor selected from compounds 1-91.

[Office Action, at page 6.] The Office Action concludes the lack of enablement rejection by stating that "it would require undue experimentation for one of skill in the art to perform the method of the claim as written." [Office Action, top of page 11.] Applicants respectfully traverse, respectfully pointing out that the claimed methods have been amended for greater clarity and particularity to comprise the use of CA IX specific aromatic and heterocyclic inhibitors that have been screened for potent and selective inhibition of CA IX; and submitting that the initial burden to challenge a presumptively enabling disclosure is upon the Examiner [MPEP § 2164.04].

The Federal Circuit quoted from In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) in In re Brana, 34 USPQ2d 1437 at 1441 (Fed. Cir. 1995) as follows:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

[Emphasis in the original.]

MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively

enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, supra; italicized emphasis in the original; underlined emphasis added.] Applicants respectfully submit that there is no reason to doubt the objective truth of statements relied upon for enabling support in the Specification for the claimed invention.

Applicants respectfully point out that at the time of filing an application, an applicant need not have any examples. An invention may be constructively reduced to practice by filing an application with no working examples at all or with paper examples. As the Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than *objective* enablement. *In re Marzocchi*, . . . , 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991); emphasis added.]

Applicants respectfully submit that the Examiner has not overcome the strong presumption that the Specification as filed is enabling, having provided insufficient "reason to doubt" the truth of the statements in the Specification relied upon for enabling support. However, even if hypothetically sufficient evidence of "reason to doubt" the truth of the statements had been provided, Applicants in the following discussion would have dispelled such a hypothetical "reason to doubt."

Applicants respectfully submit that conventional pharmacological art teaches that **inhibitor potency against, and selectivity for**, a target enzyme correlates with usefulness of that inhibitor for diagnosis and/or therapy of diseases associated with that target enzyme. The standard for enablement is whether the evidence "leads a person of ordinary skill in the art to conclude that the asserted utility **is more likely than not true**" [MPEP § 2164.07]. As shown below, there is sufficient enablement provided in the Specification for the methods of the claims as amended.

In arguing for lack of enablement, the Office Action contends that 1) "the specification does not appear to reasonably convey that the inhibitors would specifically recognize CA-IX [*sic*] in tumors, as compared to the tissues expressing other CA isozymes . . ."; 2) that lack of specificity of the inhibitors for CA IX is equivalent to lack of their correlation with diagnosis and 3) "working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention." [Office Action, bottom of page 8.]

The Examiner points out that prior art teaches that there is a relationship between CA IX expression and a tumor [Zavada et al., US Patent No. 6,027,887; Loncaster et al., Cancer Res., 61: 6394-6399 (2001)], "but that the CA IX isozyme is not the only carbonic anhydrase isozyme expressed in malignant tissue . . . [citing to Parkkila et al., PNAS, 97: 2220-2224 (2000) and Parkkila et al., Histochemical J., 27: 974-982 (1995)]. The Examiner further argues that prior art [Supuran and Scozzafava, Exp. Opin. Ther. Patents, 10(5): 575-600 (2000)] teaches that "CA isozymes . . . show high or very high and similar affinities. . . for sulphonamide inhibitors . . . [and] inhibition of CAs in sites other than the target organ/tissue may induce undesired side effects of sulphonamide drugs. . . ." [Office Action, at middle of page 10.] Applicants will address each of those points below.

A. Undue Experimentation

Applicants respectfully submit that, according to the claimed methods as amended, the Specification combined with conventional knowledge provides sufficient enablement that the inhibitors useful in the claimed methods would specifically recognize CA IX in tumors, as compared to other CA isozymes that are expressed in normal tissues. Applicants also respectfully submit that any additional experimentation necessary to perform the diagnostic/prognostic methods of the claims as amended would be merely routine.

As pointed out in the Specification at page 6, lines 19-24,

> CAs and CA-related proteins show extensive diversity in their tissue distribution, levels, and putative or established biological functions. . . . Some of the CAs are expressed in almost all tissues (CA II), while the expression of others

> appears to be more restricted (e.g., CA VI and CA VII in salivary glands. . . . The CAs and CA-related proteins also differ in kinetic properties and susceptibility to inhibitors.

As amended, each of the independent claims is now directed to methods using MN/CA IX inhibitors which have been screened in enzymatic screening assays for both potency [i.e., they inhibit MN/CA IX enzymatic activity with a K_I of less than about 50 nanomolar] and specificity [i.e., they are a more potent inhibitors of the enzymatic activity of MN/CA IX than that of CA I, CA II and CA IV]. Such enzymatic screening assays are conventional in the art of drug development.

It is conventional knowledge that certain CA isozymes are more critical in normal physiology, due to their high activity and wide distribution in many tissues. The CA isozyme that shows the highest homology with CA IX is CA VI (38.9% amino acid identity) [Specification at page 3, lines 15-16]; however, CA VI has only moderate catalytic activity, medium-low affinity for sulfonamides, and is secreted into saliva [Supuran and Scozzafava 2000, ibid, Table 1 at page 576]. CA II and CA IV are conventionally considered to be the most important CA isozymes in normal physiology [Supuran and Scozzafava 2000, ibid, page 592, bottom of left column], and are two of the three CA isozymes (other than CA IX) that are known to be highly active at physiological pH (ibid, Table 1 at page 576). Finally, as explained in the instant Specification, CA VII (the third normally-expressed CA isozyme with high activity at physiological pH) is also apparently limited in its expression to salivary glands. [Specification at page 6, lines 19-24.] Therefore, for diagnostic and prognostic purposes, preferential inhibition of CA IX over CA II and CA IV should be sufficiently enabling for CA IX selective inhibition in almost all tissues expressing CA isozymes other than CA IX.

The Patent and Trademark Office Board of Appeals and Interferences ["the Board"] stated in Ex parte Forman, 230 USPQ 546 at 547 (PTO Bd. App. & Interf. 1986) that the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . . ." As the Federal Circuit stated in In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B.

Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985): "Thus, the fact that experimentation may be complex . . . does not necessarily make it undue, if the art typically engages in such experimentation." [See also, *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.] Applicants respectfully submit that the enzymatic screening assays of the claims as amended would be routine in the art of diagnosis of cancer, and such enzymatic screening assays provide enablement sufficient for the 35 USC 112, first paragraph requirement.

B. Specificity of CA Inhibitors for CA IX

The Office Action at page 8 mistakenly argues that

> while the specification clearly teaches that the instant compounds are successful inhibitors of the claimed CA IX isozyme, as well as CA isozymes I, II and IV, the specification does not appear to provide a nexus between the use of these CA-IX [*sic*] specific inhibitors for the diagnosis of cancer. . . . [that is, such inhibitors would not] specifically recognize CA-IX [*sic*] in tumors, as compared to the tissues expressing other CA isozymes.

At page 9, the Examiner also points out that the "CA IX isozyme is not the only carbonic anhydrase expressed in malignant tissue."

Applicants respectfully disagree with the Examiner's points. The Examiner acknowledges at page 8 that "the specification teaches . . . screening assays showing the inhibition of CA-IX [*sic*] protein. . . . Moreover, the specification teaches a comparison of CA-IX [*sic*] specific inhibitor . . . with other CA isozymes. . . ." Applicants respectfully argue that the CA IX-specific inhibitors need only be shown to be **potent and preferential** CA IX inhibitors for the claimed methods to be sufficiently enabled. One of skill in the art would know that potent and preferential inhibition of a specific isozyme, rather than exclusive inhibition of a specific isozyme, can be sufficient to override the effects of possible inhibition of other isozymes, whether for therapeutic or diagnostic purposes. Applicants respectfully point out that the claimed methods of the instant invention have been amended to be directed to the use of such potent and preferential CA IX inhibitors.

Potency: It is conventional in the art of drug design to consider a lead compound with **nanomolar** inhibition of a target enzyme a potential candidate for clinical trials [see, for example, A.C. Anderson, "The Process of Structure-Based Drug Design", Chemistry & Biology, 10: 787-797 (2003) [copy attached]; flow chart depicted in Figure 1: "Is lead a nM inhibitor?", followed by "Make lead bioavailable and test for potency"].

As conceded by the Examiner at page 8, "the specification teaches the generation of 91 heterocyclic and aromatic sulfonamides and screening assays showing the inhibition of CA-IX [*sic*] protein. . . ." In fact, **Tables 1-3** from the Specification [at pages 60-61, 63-65 and 66-67] show that a number of those 91 sulfonamides are potent nanomolar inhibitors of CA IX, and the claims as amended are directed to those inhibitors that show a K_I of "less than about 50 nanomolar" of CA IX enzymatic activity. In each Table, many of the tested sulfonamides meet that criterion for potent CA IX inhibition; some show very low K_Is against CA IX [such as compounds **58** and **59** of Table 2, K_Is of 6 nM and 8 nM, respectively; Specification at page 64, lines 13-14].

Selectivity: It is also conventional knowledge that, for any particular candidate inhibitor, if its selectivity for the target isozyme versus a physiologically necessary isozyme is high (as determined by relative K_Is), that candidate inhibitor could be used at a dose low enough to inhibit the targeted isozyme in vivo with minimal side effects. Supuran and Scozzafava 2000 indicates that CA II and CA IV are the "predominant and most wide-spread isozymes in many tissues in which specific inhibition should be achieved." [op. cit., page 592, bottom of left column.]

Conventional art teaches that those carbonic anhydrases with which CA IX is the most closely related in primary sequence are most likely to share inhibitor sensitivity, and those CAs are the most important targets to test. [See, for example, discussion of kinase-selective inhibitors and their kinase isozyme targets in Knight and Shokat, Chemistry & Biology, 12: 621-637 (2005), at page 629, 2nd col. (copy attached)][2] As taught in the instant Specification at page 3, lines 15-19:

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2. The instant case of selective MN/CA IX inhibition is analogous to that of protein kinase inhibitors. Protein kinases are physiologically both ubiquitous and cancer-associated, and yet selective protein kinase inhibitors are currently considered

> The CA domain [aa 135-391; SEQ ID NO: 5] is spread over 265 aa and shows 38.9% amino acid identity with the human CA VI isoenzyme. . . . The homology between MN/CA IX and other isoenzymes is as follows: 35.2% with CA II in a 261 aa overlap . . . , 31.8% with CA I in a 261 aa overlap . . . , 31.6% with CA IV in a 266 aa overlap . . . , and 30.5% with CA III in a 259 aa overlap. . . .

However, of those isozymes VI, II, I, IV and III most closely related in primary sequence to CA IX, CA VI has only moderate catalytic activity and is only secreted by salivary glands [Specification, at page 6, lines 20-22] and CA III has very low activity [1% of CA II] and very low affinity for sulfonamides [see Table 1, Supuran and Scozzafava, 2000]. Therefore, the most important CA isozymes to test for CA IX inhibitor selectivity are isozymes CA I, II and IV.

The instant Specification teaches that, among Compounds **1-91**, several demonstrate a high preference for CA IX over any of the three other CA isozymes tested, including the physiologically most important isozymes CA II and CA IV. For example, Compounds 1, 6, 23-25 all show good selectivity ratios of CA IX over any of CA I, CA II and CA IV [Table 1, Specification at pages 60-61]. The Specification further teaches several distinctive characteristics of the CA IX active site, which direct the skilled artisan for the design of additional potent and selective CA IX inhibitors. [Please see the detailed discussion in Section IV, supra concerning such active site differences.]

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among the most promising cancer treatments [page 621, Knight and Shokat, Chemistry & Biology, 12: 621-637 (2005); copy attached]. According to Knight and Shokat, "to a first approximation, biochemical affinities predict the cellular activity of kinase inhibitors remarkably well" [page 625, top of first col.], and the "target selectivity of a kinase inhibitor is typically measured by profiling its activity against a panel of kinases in vivo." [ibid, page 629, 2nd col.]

The instant case is also analogous to the use of coxibs, to avoid the adverse effects triggered by NSAIDs related to inhibition of COX-1. COX-2 inhibitors [e.g., etoricoxib] have been found that inhibit both COX-2 (upregulated under inflammatory stimuli) and the physiologically necessary COX-1 (major isoform expressed in healthy tissue and generates prostanoids for gastric cytoprotection, maintenance of renal homeostasis, etc.); however, the inhibitors inhibit COX-2 preferentially, and at low enough doses, inhibit COX-2 without undue side effects [Riendeau et al., J Pharmac Exper Therap, 296(2): 558-566 (2001); copy attached]. That principle is well-known in the art of pharmacology.

For example, at page 9, line 1-4, the CA IX active site is described as "larger than that of the other investigated isoenzymes."

To summarize, Applicants respectfully submit that independent Claims 67, 69, 70 and 83, now amended for particularity and clarity to incorporate provisos requiring the potency and selectivity of CA IX inhibition determined by enzymatic screening assays, are shown to be enabled.

Membrane Impermeability

In addition, as explained in the instant Specification, membrane-impermeant compounds that also preferentially inhibit CA IX over CA IV are doubly selective for CA IX, as CA isozymes in the cytosol or mitochondria [e.g., CA I, CA II, CA III, CA V, CAVII] are not accessible to membrane-impermeant compounds: "Since CA IX is one of the few extracellular carbonic anhydrases, a membrane-impermeant selective inhibitor of CA IX would be doubly selective for this enzyme and thereby avoid side effects associated with nonspecific CA inhibition." [Specification at page 8, lines 10-12.] Of the sulfonamides described in the Specification, several have been shown to be both membrane-impermeant and to have potent and preferential inhibition of CA IX over CA IV [e.g., Compound **62**, at page 64, line 17]. In addition to the provisos requiring potent and specific MN/CA IX enzymatic inhibition, independent Claim 70 has been amended to be directed to methods using "cell membrane-impermeant" inhibitors of MN/CA IX, in the diagnostic/prognostic methods of the instant invention.

C. Correlation between CA IX Inhibitor Binding with Cancer Diagnosis

The Office Action states at page 8 that "the specification does not appear to provide a nexus between the use of these CA-IX [*sic*] specific inhibitors for the diagnosis of cancer." Applicants respectfully disagree, pointing out the amendments to the claims which require potent and preferential inhibition of MN/CA IX over other CA isozymes as determined by enzymatic screening assays. In addition, passages from the specification provides a clear nexus between the screened inhibitors and cancer diagnosis:

> **The inventors approached the problem of lack of selectivity of CAIs by taking advantage of features that distinguish CA IX from the other CA isoforms**. First of all, CA IX is an integral plasma membrane protein with an active site exposed on the extracellular side. In this respect, it is similar to some CAs (CA IV, CA XII and CA XIV) but differs from all other isoforms. Among these membrane-bound isoenzymes, CA IX shows some differences in the amino acid sequence of the catalytic domain that may influence the topology of the active site cavity and hence the interaction with sulfonamides. In addition, unlike the other CA isoforms, CA IX is expressed preferentially in hypoxic areas of tumors with poor prognosis.
>
> The inventors evaluated inhibition profiles of CA IX with a series of aromatic and heterocyclic compounds and found that some of them inhibit CA IX more efficiently than the other widely distributed isoforms CA I, II and IV. Several nanomolar CA IX inhibitors have been detected both among the aromatic and the heterocyclic compounds....
>
> The inventors found that some of the more bulky compounds that strongly inhibited CA IX were very weak inhibitors of CA I, II and IV, possibly due to the fact that **the CA IX active site cavity is larger than that of the other investigated isoenzymes**. The compounds of such type, identified by screening as disclosed herein, based on the selective inhibition of tumor-associated isoform CA IX may be particularly preferred CA IX specific inhibitors, that could be used in new anticancer therapies and in the diagnostic/prognostic methods of this invention.

[Summary of the Invention, at page 8, line 15 to page 9, line 7; emphasis added.] Applicants respectfully submit that in both the claims as amended, and in the Specification as filed, there is a clear nexus between the screened CA IX inhibitors and cancer diagnosis.

D. Prior Art and CA IX-Specific Inhibitors

At page 10 of the Office Action, the Examiner cites Supuran et al. [Expert Opinion on Therapeutic Patents, 10: 575-600 (2000)], particularly at page 576, 2nd col., last ¶ to page 577, 1st col., 1st two lines, arguing that "CA isozymes . . . [CA I, II, VII, IV, IX, XII, XIV, V] . . . show high or very high and similar affinities...for sulphonamide inhibitors . . . [and] inhibition of CAs in sites other than the target organ/tissue may

induce undesired side effects of sulphonamide drugs. . . ." [Office Action, middle of page 10.] Applicants respectfully point out that the sentence immediately following the Supuran 2000 passage cited by the examiner reads: "Even so, **suphonamide CAIs have a firm place in medicine**, mainly as antiglaucoma or antisecretory drugs, diuretics, as well as agents for the treatment/prevention of several neurological disorders." [Supuran and Scozzafava (2000) at page 577, 2nd col.] Applicants respectfully submit that if the side effects of such sulfonamide CAIs are acceptable for diseases such as glaucoma, that one of skill in the art could assume that similar side effects would be acceptable for sulfonamide CAIs used to treat cancer.

In part, the side effects can be limited because among the isolated normally-expressed CAs, only CA II, CA IV, CA V, and CA VII have been shown to have both "High" activity and "High" [or "Very high"] affinity for sulphonamides [ibid, Table 1, at page 576], whereas isozymes CA I, III, VI, XII, and XIV, have "Low" activity and/or "Low" affinity for sulfonamides. [The affinity of CA IX isozyme for sulfonamide inhibitors was unknown in 2000, and therefore selectivity of sulfonamide inhibitors for CA IX isozyme could not be determined. The affinity of CA XII and CA XIV was also unknown in 2000, but activity of each was identified in said Table 1 as "Low." Only CA XIII is listed in said Table I as having a "Probably high" activity but an "Unknown" affinity for sulphonamides.]

Only CA II and CA IV isozymes are described by Supuran (2000) as seeming to be "the predominant and most wide-spread isozymes in many tissues in which specific inhibition should be achieved." [Supuran (2000), page 592, sentence bridging columns.]

Of the four highly active CAs [CA II, IV, V and VII] known to have high affinity for sulfonamide inhibitors [in accordance with Table 1 of Supuran (2000)], only CA IV is membrane-bound. The Specification particularly directs: "[S]ince CA IX is one of the few extracellular carbonic anhydrases, a membrane-impermeant selective inhibitor of CA IX would be doubly selective for this enzyme and thereby avoid side effects associated with nonspecific CA inhibition." [Specification, at page 8, lines 10-12.]

The Specification also teaches that selectivity for the CA IX isozyme would be expected, based on structure-function comparisons of the different CA isozymes. As

detailed above in Section IV and discussed above in Section V, the Specification discloses a number of such structure-function comparisons. For example, the Specification states at page 9, lines 1-4; "[T]he CA IX active site cavity is larger than other investigated isoenzymes." For such reasons, one of skill in the art would reasonably expect certain organic aromatic and heterocyclic compounds to inhibit preferentially CA IX, that is, have a lower K_1 than for other isozymes. Further, the specific results of the screening assays disclosed in the Specification for the 91 heterocyclic and aromatic sulfonamides would provide depth to the disclosed structure-function comparisons.

Parkkila et al. and Multiple CA Isozyme Expression in Tumors

As mentioned above, the Examiner cites two additional Parkkila et al. articles which teach that CA IX is not the only carbonic anhydrase isozyme expressed in malignant tissue -- Parkkila et al., PNAS, 97: 2220-2224 (2000) and Parkkila et al., Histochemical J., 27: 974-982 (1995). In particular, Parkkila et al. 2000 teaches that IHC studies indicate that CA II and CA XII are expressed in renal cancer cell lines, and CA II is highly expressed in several other tumors; and Parkkila et al. 1995 teach that CA II is highly expressed in brain tumors.

The Examiner appears to be arguing that, as "CA II can not be used as a specific marker for any tumor in neuropathology . . ." [Office Action at top of page 10], that CA IX also cannot be used as a marker for any tumor in neuropathology. Applicants first respectfully counter that CA IX utility as a tumor marker is completely different from that of CA II, as CA II is considered to be a functionally important isozyme for normal physiological processes [Parkkila et al. 1995, Abstract]. The Parkkila et al. 1995 article was investigating and contradicting earlier reports which suggested that specific types of brain tumors (e.g., astrocytomas) **lost** CA II expression, and therefore CA II expression could be used to type brain tumors [ibid, page 975, top of col. 1]. Parkkila et al. 1995 states: "The present study was therefore undertaken to elucidate whether the expression of CA II **continues** in various brain tumors . . ." [sentence bridging pages 980-981 (emphasis added)], whereas the present invention concerns an established association of the **presence** of CA IX with cancer.

Unlike CA II expression in the brain, CA IX expression in the brain is abnormal, and therefore indicates a preneoplastic/neoplastic condition. The claimed methods do not propose using CA IX expression to type brain tumors. Also, the CA IX-specific inhibitors of the instantly claimed methods have been screened for both CA IX-related potency and selectivity, and therefore would be enabled to detect CA IX even in the presence of other CA isozymes expressed in tumor tissue.

With respect to the teachings of Parkkila et al., 2000, that CA XII isozyme is also expressed in renal cancer cell lines, Applicants respectfully point out that Parkkila 2000 also teach at page 2223 [paragraph bridging columns] that CA II is more likely than CA XII to play a major role in the regulation of pH homeostasis, as only CA II is a high-activity isoenzyme [specific activity of 2,500 enzyme units/mg protein for CA II, versus 200-400 units/mg for CA XII; [see also Table I of Supuran and Scozzafava 2000, op. cit. (there noted "High" activity for CA II, and "Low" activity for CA XII)]. In addition to being a low-activity isozyme, CA XII is also more weakly-expressed in tumors than CA IX, and therefore, less likely to compete with CA IX isozyme for CA inhibitors.

E. Requirement for Working Examples in an Unpredictable Art

As mentioned above, the Office Action states that working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention [Office Action, bottom of page 8]. Applicants respectfully disagree. An "applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt.'" In re Irons, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility **is more likely than not true**." [MPEP 2164.07.]

Applicants respectfully point out that at the time of filing an application, an applicant need not have any examples proving a claimed utility. An invention may be constructively reduced to practice by filing an application with no working examples at all or with paper examples. As the Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than *objective* enablement. In re Marzocchi, . . . , 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth

either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991); emphasis added.]

Applicants contend that one of skill in the art of cancer diagnosis would have a reasonable expectation that a potent CA IX-selective sulfonamide inhibitor, found to bind the CA domain in vitro with high affinity and with greater affinity for CA IX than for any of isozymes CA I, II or IV, would also selectively bind CA IX present on the surface of cells. As CA IX is considered an oncoprotein, one of skill in the art of cancer diagnosis would have a reasonable expectation that the potent CA IX-selective sulfonamide inhibitor could be used successfully in the diagnosis of preneoplastic/ neoplastic disease.

Enablement Conclusion

Applicants respectfully remind the Examiner that MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added.]

Applicants respectfully conclude that the Office Action has provided insufficient evidence of "reason to doubt" the objective truth of statements relied upon for enabling support in the Specification for the claimed invention, and that the initial burden of proof has not been carried. However, Applicants respectfully further conclude that even if that hypothetical initial burden had been shifted to the Applicants, that the Applicants would have dispelled that hypothetical burden by the above explanations and remarks.

Applicants finally conclude that the pending claims, particularly in view of the above amendments, have the sufficient support required by the enablement

requirement, and respectfully request that the Examiner withdraw the instant 35 USC 112, first paragraph rejection.

VI. 35 USC 102(b)

Claims 67-71, 76 and 78-83 stand rejected under 35 USC 102(b) as

anticipated by Zavada et al. (6,027,887, 2000, IDS).

. . . .

> . . . Zavada discloses all of the "active steps" of the claimed [*sic*] with the exception of functional limitation that the antibody is a CA-IX [*sic*] specific inhibitor. However, an antibody specific for an MN protein can be reasonably interpreted as a CA IX protein specific inhibitor because the specification defines a CA IX inhibitor as an organic compound.

[Office Action, at page 11.] Applicants respectfully point out that the claims have been amended for greater clarity and particularity to specify that the CA IX-specific inhibitor is an "aromatic or heterocyclic organic compound," and the claims clearly do not read upon a CA IX-specific antibody.

The claims have also been amended for particularity and clarity to require that the CA IX-specific inhibitors have been screened in enzymatic screening assays to be both potent CA IX inhibitors (that is, having a K_1 less than 50 nanomoler), and selective for CA IX over CA I, CA II and CA IV; or, if a membrane-impermeant compound, selective for CA IX over CA IV. The Zavada et al. '887 patent neither discloses nor claims the use of the enzymatic screening assays recited in the amended claims of the instant invention.

Applicants respectfully conclude for the reasons cited above that claims 67-71, 76 and 78-83 are not anticipated by the Zavada et al. '887 patent, and respectfully request that the Examiner withdraw the instant 35 USC 102(b) rejection.

VII. 35 USC 103

Claim 77 stands rejected under 35 USC 103(a) as

> being obvious over Zavada et al. (6,027,887, 2000, IDS) in view of Sigma® Product Information for Fluoresceine Isothiocynate (12/2000).
>
> . . . .
>
> . . . [I]It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the antibody as taught by Zavada et al. with a fluorescein isothiocynate label in view of the teachings of Sigma.

[Office Action, at pages 12-13.] Applicants respectfully point out that Claim 70, from which Claim 77 depends, has been amended for greater clarity and particularity, to specify that the CA IX-specific inhibitor is a cell membrane-impermeant aromatic or heterocyclic sulfonamide. Applicants respectfully submit that neither the Zavada '887 patent nor the Sigma® Product information, whether alone or together, render obvious the use of aromatic or heterocyclic compounds, particularly aromatic or heterocyclic sulfonamides in the claimed methods.

Applicants respectfully conclude that Claim 77 as amended is not obvious over the Zavada et al. '887 patent in view of the Sigma® Product Information for Fluoresceine Isothiocynate, and respectfully request that the Examiner withdraw the instant 35 USC 103(a) rejection.

VIII. 35 USC 101 Double Patenting Rejection

Claims 67-68 and 70-84 stand provisionally rejected under 35 USC 101, as "claiming the same invention as that of Claims 1-4, 9-10, 12-18 and 31-32 of copending Application No. 11/222,986." [Office Action, page 13.] Applicants respectfully traverse, submitting that Claims 67-68 and 70-84 of the instant application have been amended and can no longer be considered possibly identical in scope to Claims 1-4, 9-10, 12-18 and 31-32 of copending Application No. 11/222,986 ["the '986 application"].

Applicants respectfully point out that Claims 68, 70, 72, 76 and 79-84 have been amended to delete references to methods comprising the use of CA IX inhibitors to detect "activated CA IX" representing hypoxic conditions. Applicants are deferring examination of claims directed to methods of detecting "activated CA IX" to that of

copending Application No. 11/222,986. As amended, instant Claims 67-84 can not be considered identical in scope to those of the '986 application, being directed to diagnostic/prognostic methods to detect preneoplastic/neoplastic diseases comprising the use of CA IX inhibitors to detect MN/CA IX.

The Manual of Patent Examining Procedure (MPEP) provides the criterion for a double patenting rejection at MPEP § 804, subsection IIA ["Statutory Double Patenting - 35 U.S.C. 101"], which reads:

> In determining whether a statutory basis for a double patenting rejection exists, the question to be asked is: **Is the same invention being claimed twice?** 35 U.S.C. 101 prevents two patents from issuing on the same invention. **"Same invention" means identical subject matter.** *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1984); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).
>
> **A reliable test for double patenting under 35 U.S.C. 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent**. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). **Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If there is such an embodiment, then identical subject matter is not defined by both claims and statutory double patenting would not exist.** For example, the invention defined by a claim reciting a compound having a "halogen" substituent is not identical to or substantively the same as a claim reciting the same compound except having a "chlorine" substituent in place of the halogen because "halogen" is broader than "chlorine." On the other hand, claims may be differently worded and still define the same invention. Thus, a claim reciting a widget having a length of "36 inches" defines the same invention as a claim reciting the same widget having a length of "3 feet."

[MPEP § 804, IIA at pages 800-19 to 800-20; emphasis added.]

The pertinent question, according to the above passage from the MPEP, is: "**Is the same invention being claimed twice? . . . [Wherein the] '[s]ame**

invention' means identical subject matter." Applicants respectfully point out that the claimed invention and that of the '986 application are not identical.

Applicants respectfully refer to the above quote from MPEP § 804 for "[a] reliable test for double patenting under 35 U.S.C. 101 . . . [being] whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent." The answer to that test for the subject claims is yes as shown below.

Claim 1 of the '986 application reads:

> A diagnostic/prognostic method for a preneoplastic/ neoplastic disease associated with abnormal MN/CA IX expression, comprising determining whether MN/CA IX is activated in a vertebrate sample, comprising:
>
> (a) contacting said sample with a specific inhibitor of activated MN/CA IX, and
>
> (b) detecting or detecting and quantifying binding of said specific inhibitor of activated MN/CA IX in said sample;
>
> wherein binding of said inhibitor to MN/CA IX indicates that MN/CA IX is activated.

Therefore, Claims 67-68 and 70-84 of the instant invention which concern only detection of MN/CA IX, regardless of its 3-dimensional conformation or potential enzymatic activity, differ in scope from the claims of the '986 application which concern detection of only "activated CA IX." The instant claims have also been amended to be directed to aromatic and heterocyclic compounds that have been screened for specific and potent binding of MN CA IX. One of skill in the art of protein chemistry could envision aromatic and heterocyclic compounds that bind inactive CA IX protein, rather than activated CA IX.

In accordance with MPEP § 804, the instant Claims 67-68 and 70-84 can not be considered identical in scope with Claims 1-4, 9-10, 12-18 and 31-32 of the '986 application, and a 35 U.S.C. § 101 double patent rejection does not apply. Applicants respectfully request that the Examiner reconsider and withdraw the subject statutory double patenting rejection in light of the above explanations.

IX. Nonstatutory Double Patenting Rejection

Claims 74-75 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being "unpatentable over Claims 1, 3, 6-8 of copending Application No. 11/222,986. The Office Action states at page 14 that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus." Applicants respectfully submit that Claims 74-75 as amended are patentably distinct from those of the '986 application. The issue of obviousness has been addressed by the amendments made for greater clarity and particularly, which direct Claims 74-75 to methods comprising contacting a sample with a inhibitor of MN/CA IX, wherein the inhibitor is a cell membrane-impermeant aromatic or heterocyclic sulfonamide selected from Compounds 1-91, comprising contacting a sample with an inhibitor which has been screened for potency against, and selectivity for CA IX enzymatic activity.

As indicated above under "35 USC 101 Double Patenting Rejection," Applicants respectfully request that the Examiner reconsider and withdraw the subject non-statutory obviousness-type double patenting rejection in light of the amendments to the claims and the above explanations.

CONCLUSION

Applicants respectfully submit that Claims 67-70 and 72-90 as amended are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,

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